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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
FREDMAN, JEFFREY NORMAN	
ART UNIT	**PAPER NUMBER**
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/783,338	GLAZER ET AL.	
	Examiner	Art Unit	
	Jeffrey Fredman	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *December 3, 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 6-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for in vitro site directed mutagenesis of a target DNA molecule or site directed mutagenesis of a target DNA molecule ex vivo in cultured or isolated cells, but does not reasonably provide enablement for in vivo methods of site directed mutagenesis of a target DNA molecule. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

Claims 6-14 are broadly drawn to methods of site directed mutagenesis comprising a mutagen incorporated into single stranded nucleic acid that forms a triple helix with the target region which encompasses in vivo, ex vivo and in vitro methods. In fact the specification recites that the present invention provides in vivo and in vitro site directed mutagenesis of a target DNA molecule. However, as will be further discussed, there is no support in the specification and prior art for the in vivo methods, only for ex vivo or in vitro methods. The invention is an class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The unpredictability of the art and the state of the prior art

The specification recites site specific, targeted mutagenesis of the supF gene of the Lambda Phage genome from the purified DNA in an in vitro method (see specification, pages 14-18 and Table 1). The specification discloses that all except one of the 25 mutations produced by pso-AG10 is at or near the targeted T:A base pair at position 167 (see page 20). However, there is no evidence that said site-directed mutagenesis method would be operable in vivo. In example 5 of the specification, culture mouse fibroblast cells were site directed mutated by the oligonucleotide mutagen complex added to the growth medium and then UV irradiated in an ex vivo type method. However, there is no correlation between the entry of the oligonucleotide-mutagen complex in isolated cells in an ex vivo method and in vivo applications where entry into an animal is required.

There is a great deal of unpredictability in the modulation of nucleic acid interactions in vivo. Similar problems are also faced by ribozyme therapy. Uhlmann et al. (Chem. Reviews 90 : 544-584 (1990)) teach that the secondary and tertiary structure

of the target nucleic acids have a critical influence on the efficiency of the target site and that it is impossible to predict the higher order structure of the mRNA and the effect it will have on the efficacy of any potential inhibitory oligo (p. 576). Mirabelli et al (Anticancer Drug Design 6 :647-661 (1991)) teaches that we do not currently understand the precise role of nucleases, other intracellular enzymes and proteins on the stability of the ribozymes, the process by which oligonucleotides penetrate cellular membranes and distribute in cells, the non-sequence-specific-interactions that oligonucleotides can engage in both in and out of cells, and the metabolic pathways (both nuclease and non-nuclease) and metabolites that are likely to play a role in the metabolism of antisense drugs. Also underfined are the effects of specific base composition, length, chemical modifications of an oligo, and cellular parameters such as cell type, cell cycle phase and differentiation stage (Mirabelli et al, p. 651).

The post filing date art further confirms the unpredictability of this area. Puri et al (J. Biol. Chem. (2001) 276(31) :28991-28998) teaches "However, despite 40 years of research, there remain a number of impediments to the successful employment of TFOs as gene targeting reagents. Some of these obstacles reflect the properties of the oligonucleotides. Depending on the nature of the target either purine or pyrmidine TFOs can be used, but there are problems associated with each motif. Under physiological conditions purine TFOs are often subject to self structure formation which is incompatible with triplex formation. (see page 28991, column 2)". Thus, Puri expressly notes that years after Applicant's invention, the invention was still unpredictable. In fact, Puri finds that the nucleotides must be modified in a way not suggested by the application in order to achieve efficacy in what is an ex vivo assay. The complications involved in an in vivo assay would be significantly greater.

Lin et al (J. Biol. Chem. (2000) 275(50) :39117-39124) further supports the unpredictability of this art, noting that "We find that preformed triplexes on DNA that replicated following transfection are less stable than would be predicted by analyses of triplexes in vitro or on total transfected DNA (page 39118, column 1)". The entire gist of the Li paper is that triplex formation ex vivo, in cells, is dramatically different and unpredictably different from triplex formation in vitro. These differences are magnified when compared to in vivo in animal experiments, where issues of delivery, penetration, and other similar issues become relevant.

Quantity of Experimenation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied to apply this technology to in vivo methods, including the stability of the oligonucleotide-mutagen complex in blood and tissues, the distribution of oligonucleotides in tissues, the optimum mode of effective administration and the pharmocokinetics of administration. For an oligonucleotide mutagen complex, one must also consider (a) the ability of the oligonucleotide to specifically bind the target gene; (b) formation of a stable triple complex between the oligonucleotide and the target gene (note that modification of the oligonucleotide may interfere with its ability to form stable hydrogen bonds, etc.; (c) uptake of the oligonucleotide by the cell; (d) solubility of the oligonucleotide of the cell, and other such constraints. For example, with regard to the specificity issue, the AG10 oligonucleotide used in the specification is a subsequence and would hybridize to 54,417 sequences identified in Registry file. Even limiting this to humans yields 3,241 human sequences which comprise the AG10 sequence. The time table necessary to achieve efficacious administration of effective oligonucleotides, effective temperatures

and pH conditions would require a very large quantity of experimentation for in vivo applications. This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Working Examples

The specification has no working examples of in vivo site directed mutagenesis using an oligonucleotide-mutagen complex. While there are in vitro and ex vivo examples, there are no in vivo working examples.

Guidance in the Specification.

The specification provides no evidence that the disclosed effective oligonucleotide-mutagen complexes would be able to modulate nucleic acid interactions or have usefulness in sequence specific triplex formation in vivo, let alone in humans or in a living animal or in plants. The guidance provided by the specification amounts to an invitation for the skilled artisan to try and follow the disclosed instructions to make and use the claimed invention. The specification merely discloses that if necessary for activation of the mutagen, light can be delivered to cells on the surface of the body, such as skin cells (see page 12). Even if, arguendo, the oligonucleotide-mutagen complex could enter skin cells in vivo (which the prior art and specification fail to enable), these claims are not limited to skin cells. There is no support for how cells in vivo could be activated by light as disclosed. The specification discloses that light can be delivered to cells within the body by fiber optic techniques or lasers by methods known to those skilled in the art (see page 12). However, a thorough review of the prior

fails to show any enabled teachings of oligonucleotide-mutagen complex entering cells in vivo and being activated by light.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where the oligomer-mutagen complexes effects in vivo depend upon numerous known and unknown parameters such as the metabolism specific to the target DNA, potential secondary structure, oligonucleotide length and oligonucleotide chemical composition for triplex DNA, the factor of unpredictability weighs heavily in favor of undue experimentation. Further, the prior art and the specification provides insufficient guidance to overcome the art recognized problems in the use of the oligonucleotide-mutagen complexes for in vivo treatment as broadly claimed (i.e encompassing a method in any cell under any treatment in any conditions). Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Double Patenting

2. The double patenting rejection is withdrawn in view of the terminal disclaimer.

Response to Declaration

3. The Declaration under 37 CFR 1.132 filed December 3, 2002 is insufficient to overcome the rejection of claims 6-14 based upon 35 U.S.C. 112, first paragraph as set forth in the last Office action for the following reasons.

The declaration is not persuasive because it fails to properly address and overcome the factors which support the conclusion of undue experimentation based upon four thematic considerations.

First, the declaration relies significantly upon a number of references to address the conclusion of undue experimentation. None of these references were provided for consideration by the examiner and this limits the ability to assess the validity of the declaration. Also, nearly every reference cited was published after the June 24, 1993 effective filing date of this application. As MPEP 2164.05(a) notes "Publications dated after the filing date providing information publicly first disclosed after the filing date generally cannot be used to show what was known at the time of filing." So as a formal matter, these references cannot support a finding of enablement as of the time of filing.

Second, the references as discussed by the Declarant actually demonstrate the factors necessary to reach a conclusion of undue experimentation. For example, on page 3, paragraph 7 of the declaration, the Declarant notes that unmodified TFOs were ineffective in some contexts, but on page 4, paragraph 9, the Declarant tstates "it was observed that unconjugated TFOs were also capable of inducing mutations in the target gene". This is the essence of unpredictability. The ordinary practitioner would not have been aware of what conditions were necessary to reliably perform the invention in vitro,

according to this data, much less in the incredibly more complex, diverse and difficult environment of site specifically mutagenizing cells within a living animal. Many of the references, as in page 5 of the declaration, discuss a continuing improvement in the understanding of this process, from 1996 to the present day. However, since enablement is determined at the time of filing, any improved understanding is not applicable to the invention as filed on June 24, 1993.

Third, the references cited also demonstrate that the method as improved upon, as in the Chan et al paper cited on page 5 of the declaration, is not the same as the method invented and claimed on June 24, 1993. In fact, Chan et al expressly makes this point, that the methods differ, stating "The tethered donor approach differs from our previous efforts to use triplex-targeted DNA damage to induce homologous recombination. In that work, the TFO was used to introduce site-specific psoralen photoadducts to stimulate recombination between two separate supF genes. In the work presented here, no mutagen other than the triplex itself is involved, and the recombination is intended to occur not between two intact genes but between a target gene and a donor fragment tethered to the TFO. (page 11547, column 2)". So to the extent that the Chan reference demonstrates enablement of anything, it is a different method than that shown in the current specification which was neither taught nor suggested by the current specification. This same problem infects all of the other cited references because there is no discussion or evidence which demonstrates that these references operate by methodology taught in the current specification. As Chan notes

regarding the efficacy of the tethered primer method "To our knowledge, this has not been reported previously (page 11547, column 2)".

Fourth, Declarant then discusses the results of experiments in which site specific mutations are asserted to have been found in cells treated with TFOs which lacked a mutagen. This alone renders the evidence irrelevant because the experiment was not commensurate in scope with the claimed invention. Claim 6 requires that "the mutagenic oligonucleotide comprise a mutagen incorporated into a single-stranded nucleic acid (see claim 6)". The specification on pages 11 and 12 clearly indicates that the mutagen is something attached to the nucleic acid such as psoralen or an alkylating agent. The evidence presented does not include an oligonucleotide which falls within the scope of the claims. Consequently the evidence does not fall within the scope of the claim. Further, the oligonucleotides shown were not disclosed in the specification of the current claims, nor was the specific process of treatment taught by the specification. Thus, not only is the unpredictability of this invention supported by the art cited in the declaration, the declaration relies upon significant evidence which was not taught in the specification. Further, the presented evidence is not commensurate in scope with either the specification or the claims. Lastly, even if a showing of isolated mutagenesis were made, this would not provide any use since no therapeutic effect has been shown for any of the oligonucleotides, even those asserted to induce mutagenesis.

Response to Arguments

4. Applicant's arguments filed December 3, 2002 have been fully considered but they are not persuasive.

Applicant expressly relies upon the declaration to overcome the enablement rejection. Since the declaration was not found sufficient for the reasons given above, the rejection is maintained.

Conclusion

5. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is 703-308-6568. The examiner can normally be reached on 6:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 703-308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Jeffrey Fredman
Primary Examiner
Art Unit 1637

January 15, 2003